

REMARKS

Claims 1-9, 11-19 and 22 are pending in this application. Claim 22 is withdrawn. Claims 1-9 and 11-19 are under examination and stand rejected. Claim 6 is amended herein to correct a grammatical error. No new matter is added by way of this amendment. Entry of the claim amendments and reconsideration in view of the following remarks are respectfully requested.

Accompanying this response is the Declaration of Valery Rubinchik under 37 C.F.R. § 1.132 [hereinafter “the Rubinchik Declaration”]. Mr. Rubinchik currently holds the position of Senior Director, Device Technology at QLT, Inc., the assignee of the present application. A copy of Mr. Rubinchik’s *curriculum vitae* accompanies this response as Exhibit A.

Rejections under 35 U.S.C. § 103(a)

Claims 1-9 and 11-19 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Candela Corporation (WO 2003/086460) in view of Olive Oil Chemistry (U) and Bershad (U.S. Patent No. 6,096,765). Briefly, Candela Corporation is said to disclose a method of treating oily skin and sebaceous hyperplasia, including topical application of a photosensitizer in a liposome formulation or in olive oil, and irradiation at a wavelength capable of activating the photosensitizer. The fluence rate range disclosed in Candela Corporation is said to partially overlap with the claimed fluence rate range. Candela Corporation is further said to disclose the use of photosensitizers including, *inter alia*, chlorins, cyanines, purpurins and porphyrins, and BPD-MA; use of a pulsed diode laser; use of both red and blue light in ALA PDT; removal of excess photosensitizer from the lesion surface; and repetition of treatment as necessary. Olive Oil Chemistry (U) is cited as disclosing the viscosity of olive oil, which is relied upon in asserting that the olive oil formulation of Candela Corporation has a viscosity falling within the scope of claim 8. Bershad is cited as disclosing the treatment of acne with retinoids, which the Examiner asserts would be obviously substituted for salicylic acid, disclosed as a descaling agent in Candela Corp. Applicants respectfully traverse the rejections for reasons of record, as well as at least the following reasons.

As a preliminary matter, Applicants note for the record that Olive Oil Chemistry (U) is not properly citable as a reference under 35 U.S.C. §103(a) against the instant application. No evidence has been provided to show that the reference was published prior to the filing date of the instant application, which has an international filing date of 8 February 2005. The only identifiable dates for Olive Oil Chemistry are from April, 2008 or later, more than three years after the filing date of the present application. See, e.g., Olive Oil Chemistry on page 1, “this page updated 04/14/2008”; page 12, “Copyright ©April 06, 2008”; and in the footer, “12/30/08.” The Applicants would appreciate an indication that the reference is merely relied upon as evidence of the viscosity of olive oil.

While the strict teaching - suggestion - motivation (TSM) test was rejected by the Supreme Court in *KSR v. Teleflex*, there nonetheless must be an “articulated reasoning with some rational underpinning to support the legal conclusion” of obviousness. *KSR International Co. v. Teleflex, Inc.*, 82 U.S.P.Q.2d 1385, at 1396 (S. Ct. 2007). Determining if there is an articulated reason requires analysis of a number of factors, including, e.g., whether there is evidence of teaching away and whether there is a reasonable expectation of success. The Court in *KSR* re-emphasized the requirement that the Graham factors be evaluated in determining whether the claimed invention is obvious. The Graham factors require a determination of 1) the content of the prior art, 2) the level of a skill of the ordinary practitioner of the art, and 3) the nature of the differences between the prior art and the claimed invention. It must then be evaluated, as a matter of law, whether these differences, in the context of the claimed subject matter as a whole, would or would not have been obvious to the skilled artisan.

The Office has failed to establish a *prima facie* case of obviousness

In asserting that a *prima facie* case of obviousness has been established, the Office incorrectly states that Candela Corporation discloses “a fluence rate of between about 100 W/cm² and **about 40 mW/cm²** (page 4, paragraph 0012) which partially overlaps and encompasses the claimed fluence rate of between 0.1 mW/cm² to about 600 mW/cm².” (See Office Action at page 8; emphasis added.) The Office cites *In re Wertheim* for the proposition that “[i]n the case where

the claimed ranges ‘overlap or lie inside ranges disclosed by the prior art’ a *prima facie* case of obviousness exists.” *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990); MPEP § 2144.05(I).

The Office’s position relies on a mischaracterization of paragraph [0012] of Candela Corporation, which recites in pertinent part:

“The section of the skin affected by the neoplastic or non-neoplastic condition is irradiated with a beam of light that has a wavelength between about 500 nm and about 650 nm, a fluence rate between about 100 W/cm² and **about 40 MW/cm²**, and a fluence of less than about 60 J/cm².” (emphasis added)

No explanation or rationale has been provided to explain the Examiner’s conclusion that the *upper limit* of Candela Corporation’s fluence rate range, i.e., “about **40 MW/cm²**” is actually the *lower limit* of the recited range and is equivalent to **40 mW/cm²**. The Examiner’s position is not well-founded in view of the disclosure of Candela Corporation as a whole, for at least the following reasons.

First, as noted in the Rubinchik Declaration at ¶9, Candela Corporation explicitly states that fluence rates in units of “milliwatts per square centimeter” are abbreviated as “mWcm⁻²”. Thus, the drafters were familiar with and applied the standard abbreviation “mW” when referring to units of milliwatts. By contrast, Candela Corporation consistently refers to “MWcm⁻²” when discussing the high fluence rates used in their methods. In view of the consistent usage of the terms “mW” and “MW”, when referring to conventional and high fluence rate methods, respectively, one of skill in the art would reasonably conclude that these terms are not equivalent. See the Rubinchik Declaration at ¶9.

Second, the entire disclosure of Candela Corporation is related to the use of high fluence rates, i.e., fluence rates that are considerably higher than those used in conventional PDT, at relatively low total light doses, and the advantages of these conditions in avoiding side effects, such as purpura, observed under conventional conditions. See WO 2003/086460 at, e.g., page 4, lines

16-19 and page 6, lines 10-13; see also the Rubinchik Declaration at ¶5. Assuming solely for the sake of argument that the Examiner's interpretation of the disclosed fluence rate range as between 100 W/cm^2 and 40 mW/cm^2 was correct, this range overlaps with the fluence rate range that Candela Corporation describes as provided by conventional continuous wave and non-laser light sources, i.e., fluence rates of 10 to 500 milliwatts per square centimeter (page 1, lines 25-26).

Third, the exemplary conditions described by Candela Corporation include, e.g., a 10 millisecond (ms) laser pulse with a fluence of 7.5 Jcm^{-2} , which corresponds to a fluence rate of 750 Wcm^{-2} (see page 6, lines 27-31), and the use of a flashlamp to achieve desired fluence rates in the range from about 500 W/cm^2 to about 1000 W/cm^2 (page 15, lines 23-24). Candela Corporation also discloses use of a 595 nm pulsed dye laser at a fluence of 10 J/cm^2 for about 10 ms (comprised of multiple short pulses), wherein even a single 10 ms laser pulse provides a fluence rate of 1000 W/cm^2 (See WO 2003/086460 at page 15, lines 18-20). See, e.g., the Rubinchik Declaration at ¶¶10-11. Based on the Examiner's interpretation, none of these conditions would be encompassed within the fluence rate range disclosed by Candela Corporation.

In view of the foregoing remarks, the recitation of " 40 MW/cm^2 " at paragraph [0012] of Candela Corporation cannot logically be construed as the *lower end* of the high fluence rate range. While the Applicants concede there may be some question as to the intended *upper limit* of Candela Corporation's high fluence rate range, it is clear that the disclosed fluence rate of 100 W/cm^2 represents the *lower limit* of the disclosed range. See, e.g., the Rubinchik Declaration at ¶¶11-12.

Accordingly, the Office has failed to establish any overlap between the claimed fluence rate range and that disclosed by Candela Corporation. The upper limit of the claimed fluence rate range, i.e., 600 mW/cm^2 , is more than two orders of magnitude less than the minimum fluence rate of about 100 W/cm^2 disclosed by Candela Corporation. See, e.g., the Rubinchik Declaration at ¶12. Accordingly, *In re Wertheim* is inapplicable, and the alleged overlap cannot properly be relied upon to establish a *prima facie* case of obviousness.

Applicants note that the Examiner has pointed to nothing in the secondary references to Bershad and/or Olive Oil Chemistry that, when considered in combination with Candela Corporation, would change this assessment of the lack of overlap in the fluence rate ranges.

There is no motivation to modify Candela Corporation to achieve the claimed invention

As noted in the memorandum from the Deputy Commissioner, issued immediately in response to the *KSR* decision, in formulating a rejection for obviousness based on a combination of elements, it remains necessary to identify a reason why a person of ordinary skill in the art would have combined the prior art elements “in the manner claimed.” The Office has provided no motivation or suggestion to combine that would lead one of skill in the art at the time of the invention to combine the cited references in the manner proposed to achieve the instant invention.

Based on the disclosure of Candela Corporation, alone or in combination with Bershad and/or Olive Oil Chemistry, one of skill in the art would have no motivation to practice the invention as claimed. In view of Candela Corporation’s disclosure that PDT methods using high fluence rates and low overall fluences are advantageous for minimizing or preventing side effects (e.g., purpura), one of skill in the art would have neither a motivation nor a reasonable expectation of success that reduction of the fluence rate by two orders of magnitude, as discussed in detail above, would result in treatment protocol that was both effective to treat the underlying dermatological condition and also minimized or prevented side effects.

It is well settled law that in order to render a claimed invention obvious, there must be a motivation to make the suggested modifications to the cited art. “If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification.” *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); MPEP § 2143.01(V). Here, the intended purpose of Candela Corporation is to provide PDT methods that minimize or prevent the side effects seen with conventional PDT methods. Candela Corporation attributes the success of their method largely to the use of a fluence rate considerably higher than that used in conventional PDT. Thus, one of skill in the art would have no motivation to modify the conditions disclosed in Candela Corporation to

reduce the fluence rate by two orders of magnitude, because such conditions would not reasonably be expected to work for their intended purpose.

Moreover, “if the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious.” *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959); MPEP § 2143.01(VI). Modification of Candela Corporation’s high fluence rate methods to use the comparatively much lower fluence rates claimed would change their principle of operation.

The cited art fails to provide a reasonable expectation of success

As discussed in detail above, Candela Corporation attributes the success of their method to the use of high fluence rates and relatively low overall fluences, which surprisingly provide effective therapy while minimizing or preventing side effects. Given the lack of overlap between the claimed fluence rates and the range disclosed as effective by Candela Corporation, the Office has provided no basis why one of skill in the art would reasonably expect the claimed methods, which use substantially lower fluence rates than Candela Corporation, to maintain efficacy and provide an acceptable side effect profile.

In addition, the methods disclosed by Candela Corporation typically use pulsed laser irradiation, which the reference describes as surprisingly advantageous, noting that “[n]ot only are the total light doses as used in the current invention lower than those that have been used to successfully treat skin lesions in the past, but the fluence rates are considerably higher.” See WO 2003/086460 at page 6, lines 10-13; see also the Rubinchik Declaration at ¶5.

As discussed in the Rubinchik Declaration at ¶13, the results of PDT depend on the ability of photons of light to collide with drug molecules in the presence of oxygen atoms, to produce oxygen radicals that interact with tissue cells to cause apoptosis or necrosis. In view of the differences in the supply of photons, there are significant differences between continuous wave (CW) and pulsed laser PDT methods, and it is common knowledge among those of skill in the art

that conditions used in pulsed laser PDT methods (e.g., as in Candela Corporation) cannot be directly compared to CW PDT methods. Even in cases where the cumulative light dose is the same for pulsed versus CW PDT, those of skill in the art understand that the outcome of treatment is usually different and somewhat difficult to predict. See the Rubinchik Declaration at ¶13. In the instant case, where the claimed fluence rate is two orders of magnitude lower than the rate disclosed in the cited art, one of skill in the art could not reasonably predict the likelihood of success of the claimed methods.

The invention is nonobvious over Candela Corporation in view of Olive Oil Chemistry

Dependent claim 8 relates to compositions as claimed in claim 1, having a viscosity at 20°C of from about 50 cps to about 50000 cps. Olive Oil Chemistry (U) is cited as disclosing that olive oil has a viscosity of 84 cP at 20°C, which the Examiner relies upon in concluding that “when combined with olive oil the viscosity [of Candela Corp’s formulations] would be 84 centipoise (cP) at 20°C which is encompassed in the claimed range of 50 to 50,000 cps.”(See Office Action at page 5.)

Applicants note that the Examiner is making an unsupported assumption that the viscosity of Candela Corporation’s olive oil-containing emulsion would be the same as the viscosity of olive oil itself. Example 15 of Candela Corporation discloses an olive oil-containing emulsion, prepared by mixing 7.7 g of olive oil and 8 g of a surfactant and shaking by hand at room temperature, followed by addition of the photosensitizer, Hypericin (15 mg, Sigma) in 1 g of distilled water. See page 22, lines 17-20. Thus, the “olive oil” formulation disclosed by Candela Corporation is more than 50% by weight of an unspecified surfactant and water. The Office has provided no basis to conclude that the inclusion of substantial amounts of surfactant and water would have no effect on the viscosity of the olive oil formulation, as required to conclude that the emulsion inherently satisfies the viscosity limitation recited in claim 8.

Moreover, the patentability of dependent claim 8 is not predicated simply on the viscosity of the formulation applied, but on the novelty and nonobviousness of the claimed method as a whole. As discussed in detail above, independent claim 1 (from which claim 8 depends) is

nonobvious over the cited art, alone or in any combination. The Examiner has pointed to nothing in Olive Oil Chemistry that addresses the fundamental deficiencies in the Office's *prima facie* case of obviousness over Candela Corporation alone, nor is Olive Oil Chemistry properly citable for this purpose. Accordingly, the claimed invention cannot be considered obvious over Candela Corporation in view of Olive Oil Chemistry, alone or further in view of Bershad.

The invention is nonobvious over Candela Corporation in view of Bershad

Dependent claims 14-17 relate to PDT methods further comprising at least one non-photodynamic treatment for hyperactive sebaceous gland disorder, including topical treatments and/or the use of retinoid compounds.

Bershad is said to disclose treatment of acne with topically applied retinoid compositions. The Examiner asserts it is *prima facie* obvious to substitute equivalents, and therefore it would have been obvious to substitute the salicylic acid disclosed in Candela Corp. as useful for descaling the lesion with the topical retinoids of Bershad, for the predictable result of descaling the acne lesions.

The Applicants respectfully disagree, and note the Examiner has pointed to nothing in Bershad that suggests retinoids function as descaling agents, which might lead one of skill in the art to conclude retinoids would be interchangeable with salicylic acid in the methods of Candela Corporation. In addition, nothing in Bershad suggests retinoids are compatible with PDT methods.

Assuming, *arguendo*, that one of skill in the art would have considered replacing salicylic acid as a descaling agent in the methods of Candela Corporation with another agent, including, e.g., a topical retinoid agent, this does not render the instantly claimed methods obvious. Nothing in Bershad addresses the fundamental deficiencies in the Office's *prima facie* case of obviousness over Candela Corporation alone. Accordingly, the claims cannot be considered obvious over Candela Corporation in view of Bershad, alone or further in view of Olive Oil Chemistry.

In view of the foregoing remarks, Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 249692001700. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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